Acute Lymphoblastic Leukemia, Version 2.2024

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for acute lymphoblastic leukemia (ALL) provide recommendations for management of ALL, with a focus on the classification of ALL subtypes based on immunophenotype and cytogenetic/molecular markers; risk assessment and stratification for risk-adapted therapy; treatment strategies for Philadelphia chromosome (Ph)-positive and Ph-negative ALL for both adolescent and young adult and adult patients; and supportive care considerations. This selection from the NCCN Guidelines for ALL focuses on treatment recommendations for adults with newly diagnosed Ph-negative ALL based on current evidence.

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Overview

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.[1] The age-adjusted incidence rate of ALL in the United States is 1.8 per 100,000 individuals per year,[2] with approximately 6,550 new cases and 1,330 deaths estimated in 2024.[3] The median age at diagnosis for ALL is 17 years, with 53.5% of patients diagnosed at <20 years of age.[2] In contrast, 29.6% of patients are diagnosed at ≥45 years of age and only approximately 13.7% of patients are diagnosed at ≥65 years of age.[2] ALL represents 75%–80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemias among adults.[1,4]

The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children.[5] Improvements are largely owed to advances in the understanding of molecular genetics and pathogenesis of the disease, incorporation of minimal residual disease (MRD) testing, refinement of risk-adapted treatment algorithms, advent of new targeted agents, and use of allogeneic hematopoietic cell transplantation (HCT).

The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. The most common treatment regimens used in patients with ALL include modifications or variations of multiagent therapy regimens originally developed by the Berlin-Frankfurt-Münster group for pediatric patients (eg, regimens used by the Children's Oncology Group [COG] for children and adolescent and young adult [AYA] patients, or the CALGB regimen for adult patients), and the hyper-central venous access device [CVAD] regimen developed at MD Anderson Cancer Center (MDACC). In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance. Typically, induction regimens for adult ALL are also based on a backbone of vincristine, corticosteroids, and anthracyclines.

This selection from the NCCN Guidelines for ALL focuses on the treatment of newly diagnosed Philadelphia chromosome (Ph)-negative B-cell ALL (B-ALL) in adults (to view the complete and most recent version of these Guidelines, including recommendations for AYA patients, visit NCCN.org).

Frontline Therapy for Adults With Ph-Negative B-ALL

Clinical Data

CALGB 8811 Larson Regimen

The CALGB 8811 trial evaluated a 5-drug induction regimen (comprising vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide) as part of an intensive chemotherapy regimen

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for patients with previously untreated ALL (n=197; Ph-positive in 29%; median age, 32 years; range, 16–80 years).[6] Patients ≥60 years of age received a dose-adjusted regimen with a prednisone pulse for only 7 days and a 33% reduction of daunorubicin and cyclophosphamide doses. The median overall survival (OS) for all patients was 36 months, after a median follow-up of 43 months. Among patients who experienced a complete remission (CR) (85% of all patients), the median remission duration was 29 months. The estimated 3-year OS rate was higher for the subgroup of patients <30 years of age compared with those aged 30 to 59 years or patients ≥60 years of age (69% vs 39% vs 17%; $P<.001$). This was largely due to high induction-related mortality (50%) in patients ≥60 years of age, contributing to a median OS of 1 month in this population.[6] Among the subgroup of patients negative for the Philadelphia chromosome by both cytogenetics and molecular testing (n=29), median OS was 39 months and the 3-year OS rate was 62%.[6]

The CALGB 9111 study evaluated the impact of adding granulocyte colony-stimulating factor (G-CSF) after intensive therapy (CALGB 8811 Larson regimen) on neutrophil recovery in adults with ALL (n=198; median age, 35 years; range, 16–83 years).[7] Patients were randomized to receive either placebo or G-CSF beginning 4 days after induction, and the G-CSF group continued G-CSF treatment during consolidation. Although the addition of G-CSF did not result in a significant impact in OS or disease-free survival (DFS), patients in the G-CSF group had significantly shorter durations of neutropenia and thrombocytopenia, a higher CR rate, and lower induction mortality ($P=.04$) compared with patients in the placebo group.[7] Among the 41 patients ≥60 years of age randomized to G-CSF (n=21) or placebo (n=20), G-CSF use was associated with lower induction mortality (10% vs 25%); however, this did not meet statistical significance. The reduction observed with induction mortality was accompanied by a similarly nonsignificant increase in CR rate for those receiving G-CSF (81% vs 55%; $P=.1$). For the entire group ≥60 years of age, median OS was improved to 12 months, but 3-year OS remained poor at 17%.[7]

GRAALL-2005 and 2014 Regimens

Based on retrospective analyses of data from adults with B-ALL treated in clinical trials, CD20 positivity (generally defined as CD20 expression on >20% of blasts) was found to be associated with adverse outcomes measured by a higher cumulative incidence of relapse, decreased CR duration, or decreased survival.[8,9] Given the prognostic significance of CD20 expression in these patients, treatment regimens incorporating the CD20 monoclonal antibody rituximab have been evaluated.

The prospective phase II GRAALL-2003 study evaluated a pediatric-inspired regimen using intensified doses of vincristine, prednisone, and asparaginase for adolescents and adults with Ph-negative ALL (n=225; median age, 31 years; range, 15–60 years).[10] The induction regimen comprised vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide. Patients with high-risk disease and donor availability were allowed to proceed to allogeneic HCT. The event-free survival (EFS) and OS rates at 42 months were 55% and 60%, respectively. When data from patients who underwent HCT at first CR were censored, the DFS rates at 42 months were 52% for patients with high-risk disease and 68% for patients with standard-risk disease (risk assignment based on GRAALL protocol); these DFS outcomes by risk groups were similar to outcomes using the MRC UKALL/ECOG definition for risk classification.[10] Age >45 years was predictive of poorer survival outcomes on this study; the OS rate at 42 months was 41% for patients >45 years of age compared with 66% for those ≤45 years of age. Moreover, compared with patients ≤45 years of age, patients >45 years of age had a higher cumulative incidence of therapy-related deaths (23% vs 5%) and deaths in first CR (22% vs 5%).[10] Thus, it seems that the benefit of this pediatric-inspired regimen outweighed the risks for therapy-related deaths only for those patients up to 45 years of age with Ph-negative ALL.

The design of the GRAALL-2005 study was similar to the GRAALL-2003 trial, with the addition of randomized evaluation of hyperfractionated cyclophosphamide during induction and late intensification, as well as randomized evaluation of rituximab in patients with CD20-positive Ph-negative ALL (n=209; median age, approximately 40 years; range, 18–59 years).[11] The estimated 2-year EFS rate in the rituximab group was 65% (95% CI, 56%–75%) compared with the control group at 52% (95% CI, 43%–63%). After a median follow-up of 30 months, EFS was longer in the rituximab group than in the control group (hazard ratio [HR], 0.66; 95% CI, 0.45–0.98; $P=.04$).[11]

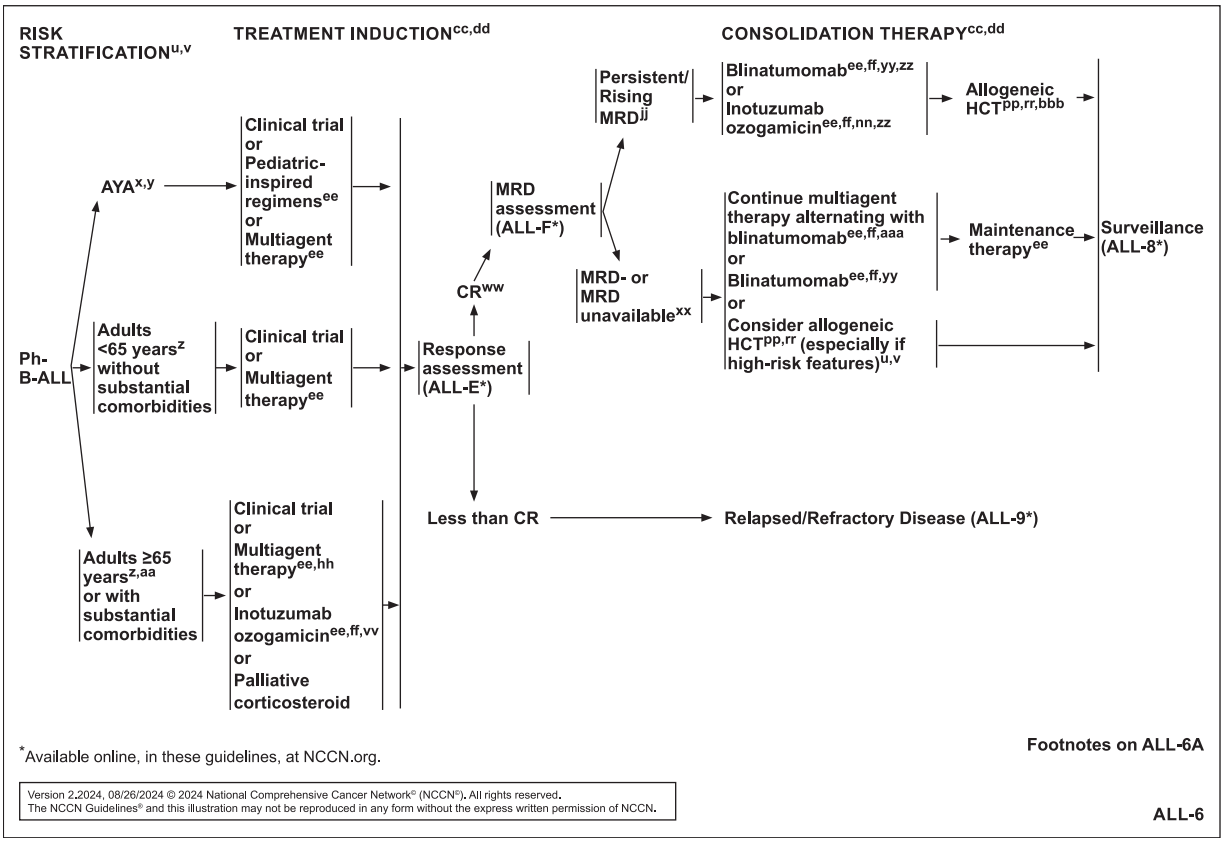


Figure 1. ALL-6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

The role of standard-dose versus hyperfractionated cyclophosphamide during first induction and late intensification in adults with newly diagnosed Ph-negative ALL was evaluated in a subsequent report from the GRAALL-2005 trial.[12] After a median follow-up of 5.2 years, randomization to the hyperfractionated cyclophosphamide arm did not increase the CR rate or prolong EFS or OS rates, and tolerability to this regimen was poor in patients ≥55 years of age.[12]

The GRAALL-2014 study aimed to improve outcomes of the GRAALL-2005 by reducing chemotherapy intensity in patients aged 45–59 years and modifying the indication for HCT to only a postinduction MRD $\geq 10^{-3}$ and/or a postconsolidation MRD $\geq 10^{-4}$.[13] Compared with GRAALL-2005, induction death rate was significantly reduced in GRAALL-2014 among patients aged 45–59 years (3% vs 11%; $P=.001$). CR rate was also higher in this age group in GRAALL-2014 (92% vs 86%, $P=.05$), attributed to a higher need for second induction due to the reduced-intensity of first induction. In light of MRD-based HCT indication, fewer patients proceeded to HCT on GRAALL-2014, leading to an increase in 3-year cumulative incidence of relapse (35% *vs* 28%; $P=.01$), though a reduction in 3-year cumulative incidence of transplant related mortality (5% vs 11%; $P<.001$) and OS (71% *vs* 64%; $P=.002$).

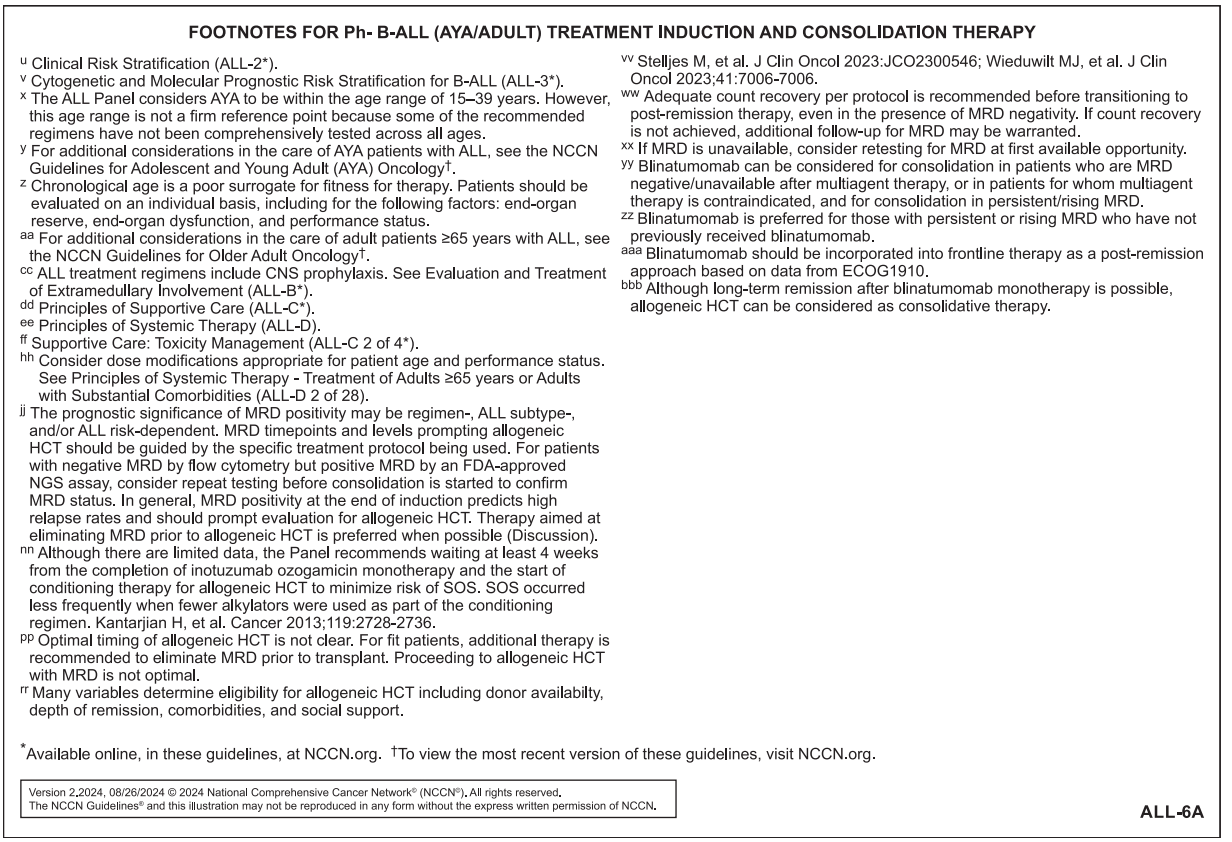
USC/MSKCC ALL Regimen Based on CCG-1882 Regimen

The USC ALL trial based on the pediatric CCG-1882 regimen studied the regimen of daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase (PEG) in patients between 18 and 60 years of age with newly diagnosed ALL (n=51).[14,15] The augmented arm included one long-lasting PEG dose in each cycle up to 6 total scheduled doses. Each dose of PEG (2,000 IU/m^2 intravenous) was preceded with hydrocortisone for hypersensitivity prophylaxis followed by 1 to 2 weeks of oral steroids. Patients on this trial received a mean of 3.8 doses per patient with 45% of patients receiving all 6 doses, while 20% of patients discontinued treatment based on toxicity. The 7-year OS was 51% (58% of these patients had Ph-negative disease) and the 7-year DFS was 58%. The dose of PEG was lower than the FDA-approved dose of 2,500 IU/m^2, and adjustments to the dosing interval were made to be ≥4 weeks. This deviated from the pediatric protocol to account for the difference in drug enzymatic activity in adults. Study data suggest that adaptation of the pediatric regimen to the adult population may be feasible with modifications to reduce toxicity.

Linker 4-Drug Regimen

Linker et al[16] evaluated an intensified chemotherapy regimen that incorporated a 4-drug induction regimen (comprising vincristine, daunorubicin, prednisone, and asparaginase) in adolescent and adult patients with ALL (n=84; Ph-positive in 16%; median age, 27 years; range, 16–59 years). The 5-year EFS and OS rates for all patients were 48% and 47%, respectively. Among the patients who experienced a CR (93% of all patients), the 5-year EFS rate was 52%. The 5-year EFS rate was 60% for the subgroup of patients without high-risk features (n=53).[16]

In a phase II study, Wieduwilt et al investigated whether the Linker 4-drug regimen could be safely intensified with the



FOOTNOTES FOR Ph- B-ALL (AYA/ADULT) TREATMENT INDUCTION AND CONSOLIDATION THERAPY

[u] Clinical Risk Stratification (ALL-2*).
[v] Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL (ALL-3*).
[x] The ALL Panel considers AYA to be within the age range of 15–39 years. However, this age range is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.
[y] For additional considerations in the care of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology†.
[z] Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.
[aa] For additional considerations in the care of adult patients ≥65 years with ALL, see the NCCN Guidelines for Older Adult Oncology†.
[cc] ALL treatment regimens include CNS prophylaxis. See Evaluation and Treatment of Extramedullary Involvement (ALL-B*).
[dd] Principles of Supportive Care (ALL-C*).
[ee] Principles of Systemic Therapy (ALL-D).
[ff] Supportive Care: Toxicity Management (ALL-C 2 of 4*).
[hh] Consider dose modifications appropriate for patient age and performance status. See Principles of Systemic Therapy - Treatment of Adults ≥65 years or Adults with Substantial Comorbidities (ALL-D 2 of 28).
[jj] The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. For patients with negative MRD by flow cytometry but positive MRD by an FDA-approved NGS assay, consider repeat testing before consolidation is started to confirm MRD status. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt evaluation for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible (Discussion).
[nn] Although there are limited data, the Panel recommends waiting at least 4 weeks from the completion of inotuzumab ozogamicin monotherapy and the start of conditioning therapy for allogeneic HCT to minimize risk of SOS. SOS occurred less frequently when fewer alkylators were used as part of the conditioning regimen. Kantarjian H, et al. Cancer 2013;119:2728-2736.
[pp] Optimal timing of allogeneic HCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplant. Proceeding to allogeneic HCT with MRD is not optimal.
[rr] Many variables determine eligibility for allogeneic HCT including donor availabilty, depth of remission, comorbidities, and social support.
[vv] Stelljes M, et al. J Clin Oncol 2023:JCO2300546; Wieduwilt MJ, et al. J Clin Oncol 2023;41:7006-7006.
[ww] Adequate count recovery per protocol is recommended before transitioning to post-remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted.
[xx] If MRD is unavailable, consider retesting for MRD at first available opportunity.
[yy] Blinatumomab can be considered for consolidation in patients who are MRD negative/unavailable after multiagent therapy, or in patients for whom multiagent therapy is contraindicated, and for consolidation in persistent/rising MRD.
[zz] Blinatumomab is preferred for those with persistent or rising MRD who have not previously received blinatumomab.
[aaa] Blinatumomab should be incorporated into frontline therapy as a post-remission approach based on data from ECOG1910.
[bbb] Although long-term remission after blinatumomab monotherapy is possible, allogeneic HCT can be considered as consolidative therapy.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

ALL-6A

Figure 2. ALL-6A. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

addition of PEG, cyclophosphamide, rituximab, dasatinib, and intrathecal liposomal cytarabine in adults with ALL or lymphoblastic lymphoma (n=29; median age, 28 years; range, 20–54 years).[17] The CR rate for ALL was 88%. For Ph-negative B-ALL (n=16), the CR rate was 86%, and for Ph-positive B-ALL (n=7), the CR rate was 88%.[17] With a median follow-up of 32 months, the 2-and 3-year EFS were 59%, and EFS was similar for B-ALL, T-ALL, lymphoblastic lymphoma, Ph-negative B-ALL, and Ph-positive B-ALL.[17]

Mrc Ukall Xii/Ecog E2993

In one of the largest multicenter prospective trials conducted to date (MRC UKALL XII/ECOG E2993 study), adolescent and adult patients with newly diagnosed disease (n=1,521; aged 15–59 years) received induction therapy consisting of vincristine, daunorubicin, prednisone, and L-asparaginase for 4 weeks (phase I) followed by cyclophosphamide, cytarabine, oral mercaptopurine (6-MP), and intrathecal methotrexate for 4 weeks (phase II).[18] After completion of induction therapy, patients who experienced a CR received intensification therapy with 3 cycles of high-dose methotrexate (with standard leucovorin rescue) and L-asparaginase. After intensification, those <50 years of age who had an HLA-compatible sibling underwent allogeneic HCT; all others were randomized to receive autologous HCT or consolidation/maintenance treatment.[18] For Ph-negative disease, "high-risk" disease was defined as having any of the following factors: aged ≥35 years; time to CR >4 weeks; or elevated white blood cell (WBC) count ($>30 \times 10^9$/L for B-cell lineage; $>100 \times 10^9$/L for T-cell lineage). All other patients with Ph-negative disease were considered to have standard-risk disease. The 5-year OS rate for all patients with Ph-negative ALL was 41%; the OS rates for the subgroups with standard-risk (n=533) and high-risk disease (n=590) were 54% and 29%, respectively.[18]

Hyper-CVAD With or Without Rituximab or Blinatumomab

The hyper-CVAD regimen constitutes another commonly used ALL treatment regimen for adults. A phase II study from MDACC evaluated hyper-CVAD in adolescents and adults with previously untreated ALL (n=288; median age, 40 years; range, 15–92 years; Ph-positive in 17%).[19] The median OS for all patients was 32 months and the 5-year OS rate was 38%, with a median follow-up of 63 months. Among the patients with Ph-negative ALL (n=234), the 5-year OS rate was 42%.[19] Among patients who experienced a CR (92% of all patients), the 5-year CR duration rate was 38%.[19] Death during induction therapy occurred in 5% of patients and was more frequent among patients ≥60 years of age. The 5-year OS in patients ≥60 years of age was 17%.[19] A subsequent retrospective review from the same institution suggested that this may be related to higher rates of death in remission (34%) relative to patients <60 years of age (7%).[20]

A phase II study from MDACC evaluated hyper-CVAD with or without rituximab in patients with newly diagnosed Ph-negative B-ALL (n=282; median age, 41 years; range, 13–83 years).[21] Among the subgroup of patients with CD20-positive ALL who were treated with hyper-CVAD combined with rituximab, the 3-year CR duration and OS rates were 67% and 61%, respectively. In addition, among patients <60 years of age with CD20-positive

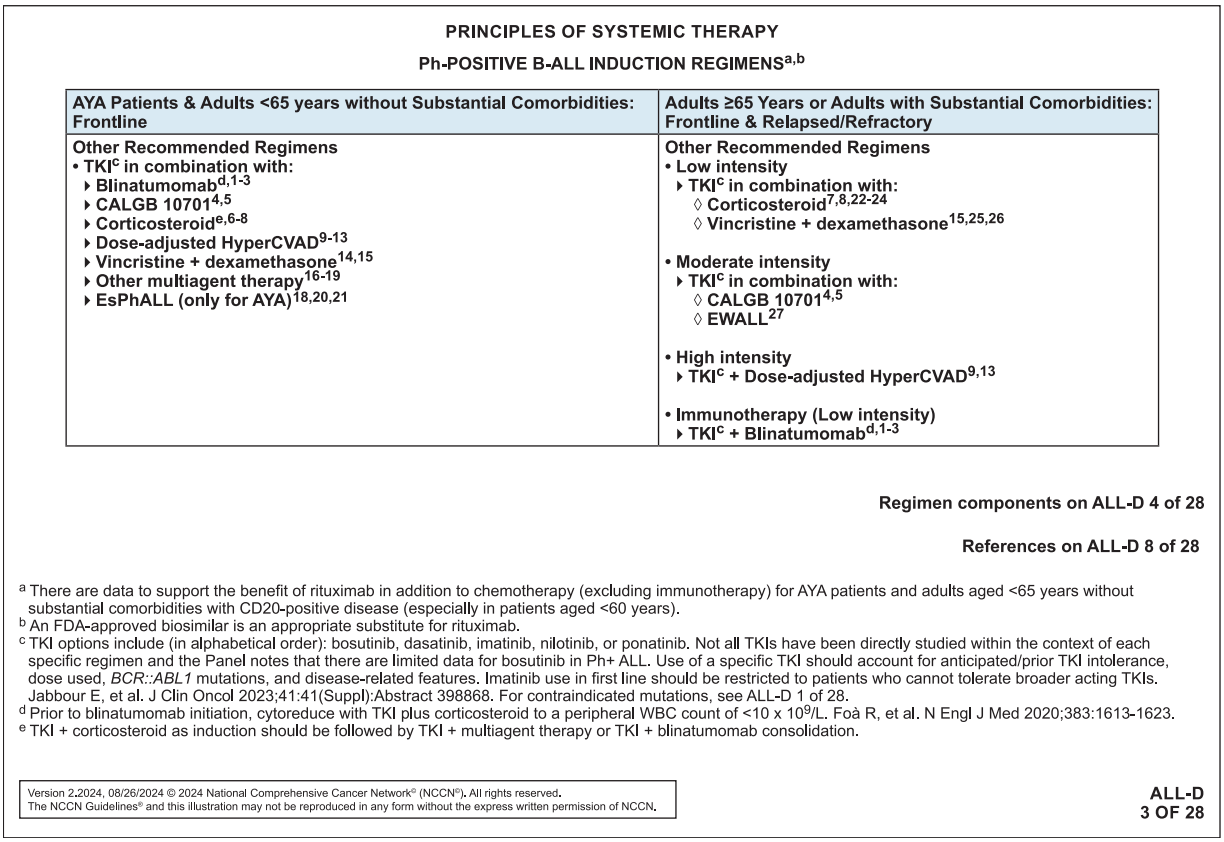


Figure 3. ALL-D 3 of 28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

disease, modified hyper-CVAD plus rituximab resulted in a significantly improved CR duration (70% vs 38%; $P<.001$) and OS rate (75% vs 47%; $P=.003$) compared with the standard hyper-CVAD regimen without rituximab.[21] No significant differences in outcomes with the addition of rituximab were noted for the subgroup of patients with CD20-negative disease. Notably, patients ≥60 years of age with CD20-positive disease demonstrated higher rates of MRD negativity with the inclusion of rituximab; however, this did not translate into a survival benefit, again largely due to increased mortality in CR. It is worth noting that this high rate of death in CR for patients ≥60 years of age may relate to anthracycline intensification as opposed to rituximab.[22]

Another phase II study from MDACC evaluated hyper-CVAD and sequential blinatumomab in patients with newly diagnosed Ph-negative B-ALL (n=38; median age, 37 years).[23] Treatment consisted of 4 cycles of hyper-CVAD followed by 4 cycles of blinatumomab consolidation. Maintenance consisted of 15 cycles of alternating POMP (6-MP, vincristine sulfate, methotrexate, and prednisone) for 3 cycles and blinatumomab for 1 cycle. Three-year relapse-free survival (RFS) was estimated at 73%, with no relapses more than 2 years from the start of therapy. Grade 3 cytokine release syndrome occurred in one patient (3%), while 4 patients (11%) had grade 3 neurologic events related to blinatumomab.

GRAALL-SA1 Regimen

In an effort to decrease toxicity, the GRAALL-SA1 study compared the efficacy and toxicity of pegylated liposomal doxorubicin (Peg-Dox) to continuous infusion doxorubicin (CI-Dox) in patients ≥55 years of age with ALL.[24] In this moderate-intensity regimen containing vincristine, dexamethasone, and cyclophosphamide, patients were randomized to receive either CI-Dox (n=31; 12 mg/m^2/day) or Peg-Dox (n=29; 40 mg/m^2).[24] Compared with the CI-Dox arm, the Peg-Dox arm was significantly associated with reduced toxicity and fewer infections, but there was no survival benefit: the induction mortality rate was 8% (CI-Dox arm, 7% vs Peg-Dox arm, 10%), the frequency of refractory disease after induction was 10% (CI-Dox arm, 17% vs Peg-Dox arm, 3%; $P=.1$), and the CR rate was 82% (CI-Dox arm, 90% vs Peg-Dox arm, 72%; $P=.1$).[24] At 2 years, the estimated death in CR was 26.5% (CI-Dox arm, 37% vs Peg-Dox arm, 19%), and the OS and EFS rates were statistically similar at 35% and 24% in the CI-Dox and Peg-Dox arms, respectively.[24]

GMALL Regimen

In a prospective trial, the GMALL group evaluated the efficacy of a moderate-intensity regimen in adults aged 55 to 85 years with Ph-negative ALL (n=268).[25] The induction therapy consisted of induction I (dexamethasone, vincristine, idarubicin) and induction II (cyclophosphamide, cytarabine), with rituximab added for patients with CD20-positive disease. The original treatment protocol (group 1) was modified to evaluate central nervous system (CNS) prophylaxis with liposomal cytarabine and alternative consolidation with asparaginase (group 2); and after induction, 1 cycle with 500 U/m^2 PEG was scheduled to evaluate feasibility (group 3). The reported overall CR rate was 76% (n=203), and the CR rates in groups 1, 2, and 3 were 72%, 86%, and 82%, respectively.[25] The 5-year OS rate

PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL INDUCTION COMPONENTS[a,b,f,g,h,i]

AYA Patients without Substantial Comorbidities: Frontline	Adults <65 years without Substantial Comorbidities: Frontline	Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline & Relapsed/Refractory
Other Recommended Regimens		
• **Blinatumomab[d] + TKI[c,1-3]**		
• **CALGB 10701[4,5] + TKI[c]:** Cyclophosphamide, daunorubicin, dexamethasone, vincristine		
• **Corticosteroid[e] + TKI[c,6-8]**		• **Corticosteroid + TKI[c,7,8,22-24]**
• **EsPhALL[19,20,21] + TKI[c]:** Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, mercaptopurine, pegaspargase, thioguanine, vincristine		• **EWALL[27] + TKI[c]:** Cyclophosphamide, dexamethasone, vincristine
• **Dose-adjusted HyperCVAD[9-13] + TKI[c]:** Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine		
• **Other multiagent therapy[16-19] + TKI[c]:** Cyclophosphamide, daunorubicin, prednisone, vincristine		
• **Vincristine + dexamethasone + TKI[c,14,15,25,26]**		

References on ALL-D 8 of 28

[a] There are data to support the benefit of rituximab in addition to chemotherapy (excluding immunotherapy) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[b] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[c] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. J Clin Oncol 2023;41(Suppl):Abstract 398868. For contraindicated mutations, see ALL-D 1 of 28.
[d] Prior to blinatumomab initiation, cytoreduce with TKI plus corticosteroid to a peripheral WBC count of <10 x 10^9/L. Foà R, et al. N Engl J Med 2020;383:1613-1623.
[e] TKI + corticosteroid as induction should be followed by TKI + multiagent therapy or TKI + blinatumomab consolidation.
[f] All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
[g] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.
[h] For patients who develop hypersensitivity to Escherichia coli-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[i] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤21 years for more sustained asparaginase activity. Silverman LB, et al. Blood 2016;128:175; Angiolillo AL, et al. J Clin Oncol 2014;32:3874-3882.

ALL-D 4 OF 28

Figure 4. ALL-D 4 of 28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

was 23%, and the 2-year OS rates observed in groups 1 and 2 were 33% and 52%, respectively.[25] A major finding from this study included the importance of the ECOG performance status *before* the onset of ALL (ECOGb) at predicting induction mortality. Patients with an ECOGb score ≥2 correlated with higher induction mortality rates compared with those with an ECOGb score of 0 to 1 (53% vs 7%, respectively; $P<.0001$).[25] In addition, the study showed that consolidation with native *Escherichia coli* asparaginase and PEG was feasible and well tolerated and was associated with improvements in CR rates and 2-year OS in this aged 55 to 85 years patient subset.[25]

PETHEMA-Based Regimen

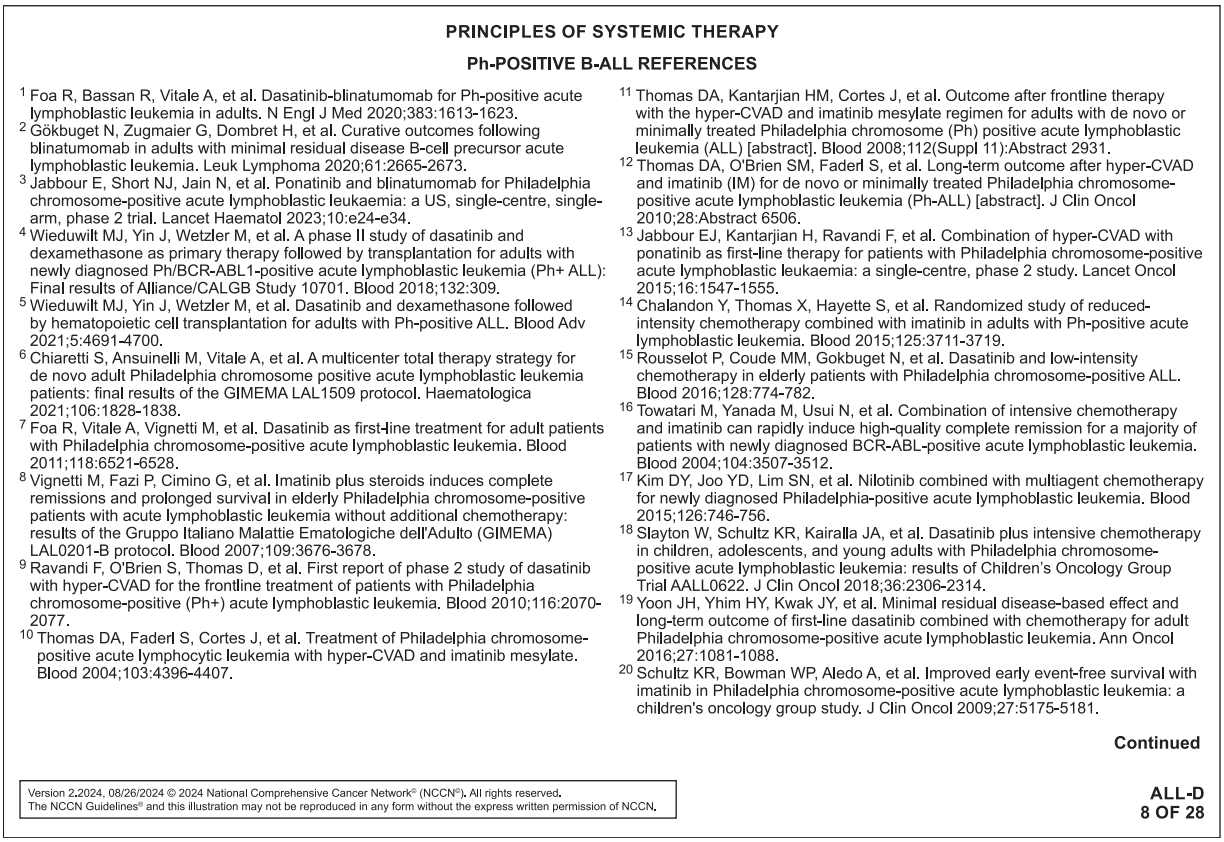
The Spanish PETHEMA group conducted phase II prospective studies in patients aged 56 to 79 years with Ph-negative ALL (ALLOLD07; n=56).[26,27] The ALLOLD07 protocol was based on a protocol from EWALL, and treatment comprised a 4-week induction with dexamethasone, vincristine, idarubicin, cyclophosphamide, and cytarabine, followed by consolidation with intermediate-dose methotrexate and native *E. coli* asparaginase. The CR rate was 74% with an early death rate of 13%. The median DFS was 8 months with a median OS of 12 months. This trial included other adapted regimens for Ph-positive ALL and mature B-ALL groups, but the outcomes were poorest in the Ph-negative ALL group.[27]

Modified DFCI 91-01 Protocol

A retrospective analysis examined the efficacy of a modified version of a DFCI pediatric protocol, DFCI 91-01,[28,29] in adults with newly diagnosed ALL (n=51; age range, 60–79 years).[30] Induction consisted of dexamethasone (in place of prednisone), doxorubicin, cytarabine, and reduced doses of methotrexate, vincristine, and native asparaginase. For patients who achieved CR, the median time to recurrence was 30 months (range, 1–94 months).[30] In patients with Ph-negative disease (n=35), the CR rate was 71%, with induction mortality and primary refractory rates of 20% and 9%, respectively.[30] The 5-year DFS rate among those achieving CR was 57.4% (95% CI, 32.8%–75.8%), while the overall estimated 5-year OS was 40.5% (95% CI, 20%–60.2%).[30]

Low-Intensity Chemotherapy and Corticosteroids

For adults who are older with ALL who may also have multiple comorbidities, the utility of traditional chemotherapy backbones based on vincristine, corticosteroids, and an anthracycline is limited largely due to treatment-related toxicities.[31] Attempts to identify optimal therapy in this population have included adaptations of palliative regimens including vincristine and corticosteroids, and POMP.[32–35] Although these regimens are unlikely to generate cure, they can palliate the disease and extend survival, with clinical outcomes similar to those achieved with more intensive protocols. It is important to note that adults who are older with ALL and multiple comorbidities have not typically qualified for clinical trials. To improve clinical outcomes, trials designed specifically for this population are needed. These should include novel, personalized approaches based on immunophenotype and/or genetic mutation status.



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ALL-D
8 OF 28

Figure 5. ALL-D 8 of 28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

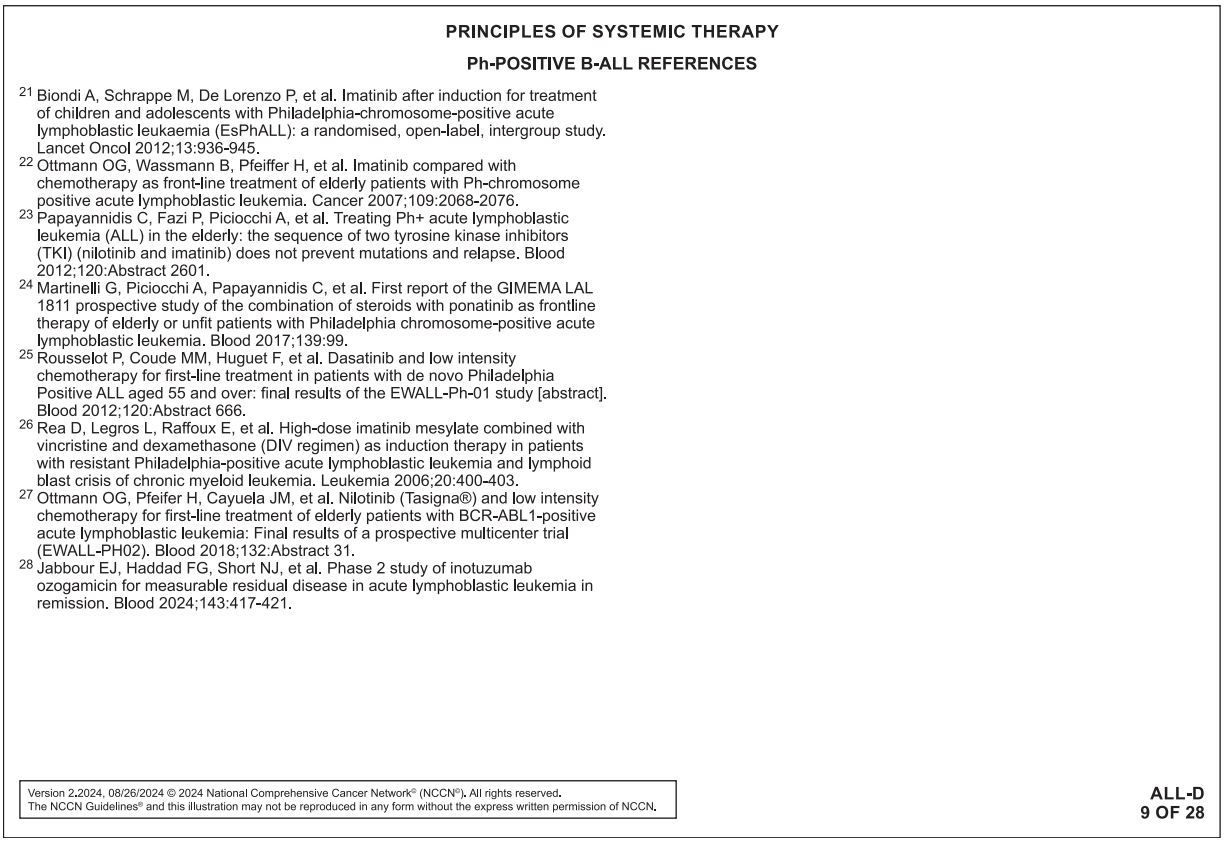
Inotuzumab Ozogamicin

In a phase II study, the efficacy and safety of the antibody drug conjugate inotuzumab ozogamicin (InO), combined with low-intensity chemotherapy (mini-hyper-CVD) was evaluated in adults with a median age of 68 years with newly diagnosed Ph-negative ALL and an ECOG performance status ≤3 (n=52; interquartile range, 64–72 years).[36] Compared with hyper-CVAD, mini-hyper-CVD has no anthracycline and is composed of reduced doses of dexamethasone (50% reduction), methotrexate (75% reduction), and cytarabine (given every 12 hours at 0.5 g/m^2 on days 2 and 3). In this study, InO was given on day 3 of the first 4 courses at 1.3–1.8 mg/m^2 for cycle 1, followed by 1.0–1.3 mg/m^2 for subsequent cycles.[36] In addition, maintenance therapy with dose-reduced POMP was given for 3 years. With a median follow-up of 29 months, the 2-year progression-free survival was 59% (95% CI, 43%–72%).[36] Some of the most frequent grade 3 and 4 adverse events were prolonged thrombocytopenia (81%), infections during induction and consolidation (52% and 69%, respectively), and hyperglycemia (54%).[36] In this study, sinusoidal obstruction syndrome (SOS) occurred in 4 patients (8%).

A phase II study evaluated InO monotherapy in 26 patients (median age, 46 years; range, 19–70 years) patients with B-cell ALL in CR1 or beyond with positive MRD ($\geq 1 \times 10^{-4}$).[37] After a median of 3 cycles (range, 1–6 cycles), 69% of patients experienced MRD negativity. Two-year RFS and OS rates were 54% and 60%, respectively. Eight percent of patients developed SOS, and the remainder of adverse events were noted to be low grade.

In the phase II INITIAL-1 trial, InO combined with dexamethasone is being investigated as an induction regimen for patients ≥55 years of age (n=43; median age, 64 years; age range, 56–80 years) with newly diagnosed Ph-negative B-ALL.[38] Up to 3 cycles of InO/dexamethasone induction were given, followed by up to 6 cycles of GMALL consolidation adapted by age and maintenance therapy. All patients achieved CR/CR with incomplete hematologic recovery (CRi) following 2–3 cycles of InO/dexamethasone. Following cycle 2, 53% of patients experienced MRD negativity, while 30% experienced MRD negativity after cycle 3. With a median follow-up of 2.7 years, 1-year EFS and OS were 88% and 91%, respectively. Three-year EFS and OS were 55% and 73%, respectively.

In the ongoing phase II Alliance A041703 trial, the chemotherapy-free regimen of InO for induction followed by blinatumomab consolidation is being investigated in patients ≥60 years of age (n=33; median age, 71 years; range, 60–84 years) with newly diagnosed Ph-negative B-ALL with no plans for allogeneic HCT.[39] Induction course IA included InO at a dose of 0.8 mg/m^2 on day 1 followed by 0.5 mg/m^2 on days 8 and 15 of a 21-day cycle. Those with adequate cytoreduction, defined as reduction of bone marrow blasts by ≥50% or cellularity ≤20%, went on to receive either induction IB (InO 0.5 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) if CR/CRi was achieved or induction IC (InO 0.8 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) if having not achieved CR/CRi. Those with inadequate cytoreduction to induction IA or those without events in induction IA, IB, or IC began blinatumomab consolidation. Those experiencing CR/CRi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ALL-D
9 OF 28

Figure 6. ALL-D 9 of 28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

with InO received a total of 3 28-day cycles of blinatumomab, while all others received a total of 4 cycles. The cumulative CR rate through induction InO courses was 85% and for blinatumomab consolidation was 97%. With a 22-month median follow-up, 1-year EFS was 75% (95% CI, 61%–92%) and 1-year OS was 84% (95% CI, 72%–98%). [39]

A separate phase II MDACC study evaluated the use of mini-hyper-CVD and InO with or without blinatumomab in patients ≥60 years of age with newly diagnosed Ph-negative B-ALL.[40] Treatment consisted of 4 cycles of mini-hyper-CVD with InO followed by 4 cycles of blinatumomab consolidation. Maintenance therapy consisted of 3 cycles of POMP alternating with 1 cycle of blinatumomab for a total of 12 cycles. Five-year progression-free survival was 44%. The most common grade 3–4 events were hematologic. Six patients (8%) developed SOS, 4 of which were fatal.

Blinatumomab

Blinatumomab, a bispecific T-cell engager antibody targeted against CD19, has shown promising clinical efficacy as a means of eradicating persistent MRD following upfront chemotherapy. In a multicenter, single-arm, phase II study, Topp et al[41] evaluated the efficacy of blinatumomab in patients with MRD-positive Ph-negative B-ALL (n=21; age range, 20–77 years). Patients were considered to have MRD-positive disease if they had never achieved MRD negativity before blinatumomab or had experienced a hematologic CR with MRD $\geq 10^{-4}$. After blinatumomab treatment, 16 of 20 patients with evaluable data were determined to have experienced MRD negativity at a detection threshold of 10^{-4}.[41] After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.[42] Gökbuget et al[43] examined the efficacy of blinatumomab in an expanded cohort (n=116) using a higher threshold for MRD positivity (hematologic CR with MRD $\geq 10^{-3}$). After one 28-day cycle of blinatumomab, 88 of 113 patients with evaluable data achieved a complete MRD response, and the RFS rate at 18 months was 54%.[43] In both of these trials, most patients achieving MRD negativity after blinatumomab proceeded to allogeneic HCT, establishing blinatumomab as an effective "bridge to transplant" in patients with MRD-positive disease. Subsequent studies of blinatumomab evaluated its ability to induce CR (including rapid MRD-negative responses) in patients with R/R B-precursor ALL.[44–46] In March 2018, the FDA approved blinatumomab use for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second CR with MRD defined as disease ≥0.1%.

ECOG-ACRIN E1910 Regimen

In contrast to prior studies investigating blinatumomab as a means of eradicating MRD during or after multiagent therapy, this phase III trial investigated whether blinatumomab could improve outcomes in patients receiving chemotherapy who had experienced MRD negativity (<0.01%).[47] Patients with newly diagnosed Ph-negative B-ALL between the ages of 30 to 70 years initially received multiagent induction therapy with a Berlin-Frankfort-Münster–like regimen adapted from E2993/UKALLXII. PEG was added for patients <55 years of age and rituximab was added for CD20 positivity. After induction, patients who

PRINCIPLES OF SYSTEMIC THERAPY

GENERAL CONSIDERATIONS

- **The ALL Panel considers AYA to be within the age range of 15–39 years. However, this age range is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.**
- **For infection risk, monitoring, and prophylaxis recommendations for immune and targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections†.**
- **For toxicity management for blinatumomab, inotuzumab ozogamicin, brexucabtagene autoleucel, and tisagenlecleucel, see Supportive Care ALL C 2 of 4*.**
- **Although there are limited data, the Panel recommends waiting at least 4 weeks from the completion of inotuzumab ozogamicin monotherapy and the start of conditioning therapy for allogeneic HCT to minimize risk of sinusoidal obstruction syndrome (SOS). SOS occurred less frequently when fewer alkylators were used as part of the conditioning regimen. Kantarjian H, et al. Cancer 2013;119:2728-2736**
- **Leucovorin is always used in combination with high-dose methotrexate.**
- **Mesna is always used in combination with ifosfamide and used in combination with cyclophosphamide as clinically indicated.**

Mutation Profile Principles

TREATMENT OPTIONS BASED ON *BCR::ABL1* MUTATION PROFILE

Therapy	Contraindicated Mutations
Bosutinib	*T315I, V299L, G250E*, or *F317L*
Dasatinib	*T315I/A, F317L/V/I/C*, or *V299L*
Nilotinib	*T315I, Y253H, E255K/V, or F359V/C/I* or *G250E*
Ponatinib	None

- **Mutations contraindicated for imatinib are too numerous to include. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.**
- **Nilotinib may be preferred over bosutinib in patients with *F317L* mutation.**
- **Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or progressive disease (PD) on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details. The PhALLCON study suggests improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. J Clin Oncol 2023;41(Suppl):Abstract 398868.**
- **For patients receiving mercaptopurine (6-MP), consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. Testing for both *TPMT* and *NUDT15* variant status should be considered, especially for patients of East Asian descent. Relling MV, et al. Clin Pharmacol Ther 2019;105:1095-1105.**

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*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

Figure 7. ALL-D 1 of 28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

experienced a CR/CRi remained on study and proceeded to intensification with high-dose methotrexate and pegaspargase for CNS prophylaxis. Thereafter, MRD status was assessed by 6-color flow cytometry. Patients were randomized to receive either 4 cycles of consolidation chemotherapy or 2 cycles of blinatumomab followed by 2 cycles of consolidation chemotherapy, followed by a third cycle of blinatumomab, followed by another cycle of consolidation chemotherapy, and finally a fourth cycle of blinatumomab. However, after the FDA approval of blinatumomab for patients with MRD-positive disease, those with MRD positivity in the trial were no longer randomized and assigned to the blinatumomab arm. All patients received POMP maintenance therapy for a total of 2.5 years. Patients were referred for allogeneic HCT at provider discretion. For the entire cohort, CR/CRi rate after induction was 81%. For those who experienced MRD negativity, the addition of blinatumomab led to significant improvement in outcomes. Three-year OS in the blinatumomab group was 85% compared with 68% for the chemotherapy-alone group (P=.002) and 3-year RFS was 80% vs 64%, respectively (HR, 0.53; 95% CI, 0.32–0.87).

Based on these data, in June 2024, the FDA expanded the approval of blinatumomab to include adult and pediatric patients ≥1 month with Ph-negative B-ALL in the consolidation phase of multiphase chemotherapy.

Hematopoietic Cell Transplantation

For adults with Ph-negative ALL in first CR, allogeneic HCT may be considered for high-risk cases - particularly for patients with disease that is MRD positive any time after induction; or patients with elevated WBC counts; or patients with B-ALL and poor-risk cytogenetics [eg, hypodiploidy, *KTM2A (MLL)* rearrangement] at diagnosis. A large multicenter trial (LALA-94 study) evaluated the role of postinduction HCT as one of the study objectives in adolescent and adult patients with ALL receiving therapy for previously untreated ALL (n=922; median age, 33 years; range, 15–55 years).[48] Patients were stratified into 4 risk groups: (1) Ph-negative standard-risk disease [defined as achievement of CR after 1 course of chemotherapy; absence of CNS disease; absence of t(4;11), t(1;19), or other 11q23 rearrangements; WBC count $<30 \times 10^9$/L]; (2) Ph-negative high-risk ALL (defined as patients with non–standard-risk disease and without CNS involvement); (3) Ph-positive ALL; and (4) evidence of CNS disease. After induction therapy, patients with Ph-negative high-risk ALL were eligible to undergo allogeneic HCT if a matched sibling donor was available; those without a sibling donor were randomized to undergo autologous HCT or chemotherapy alone.[48] Among the subgroup of patients with Ph-negative high-risk ALL (n=211), the 5-year DFS and OS rates were 30% (median, 16 months) and 38% (median, 29 months), respectively. Based on intent-to-treat analysis, outcomes in patients with Ph-negative high-risk ALL were similar for autologous HCT (n=70) and chemotherapy alone (n=59) in terms of median DFS (15 vs 11 months), median OS (28 vs 26 months), and 5-year OS rate (32% vs 21%).[48] Outcomes were improved in patients with Ph-negative high-risk ALL and those with CNS involvement allocated to allogeneic HCT. The median DFS was 21 months for these patients, and the

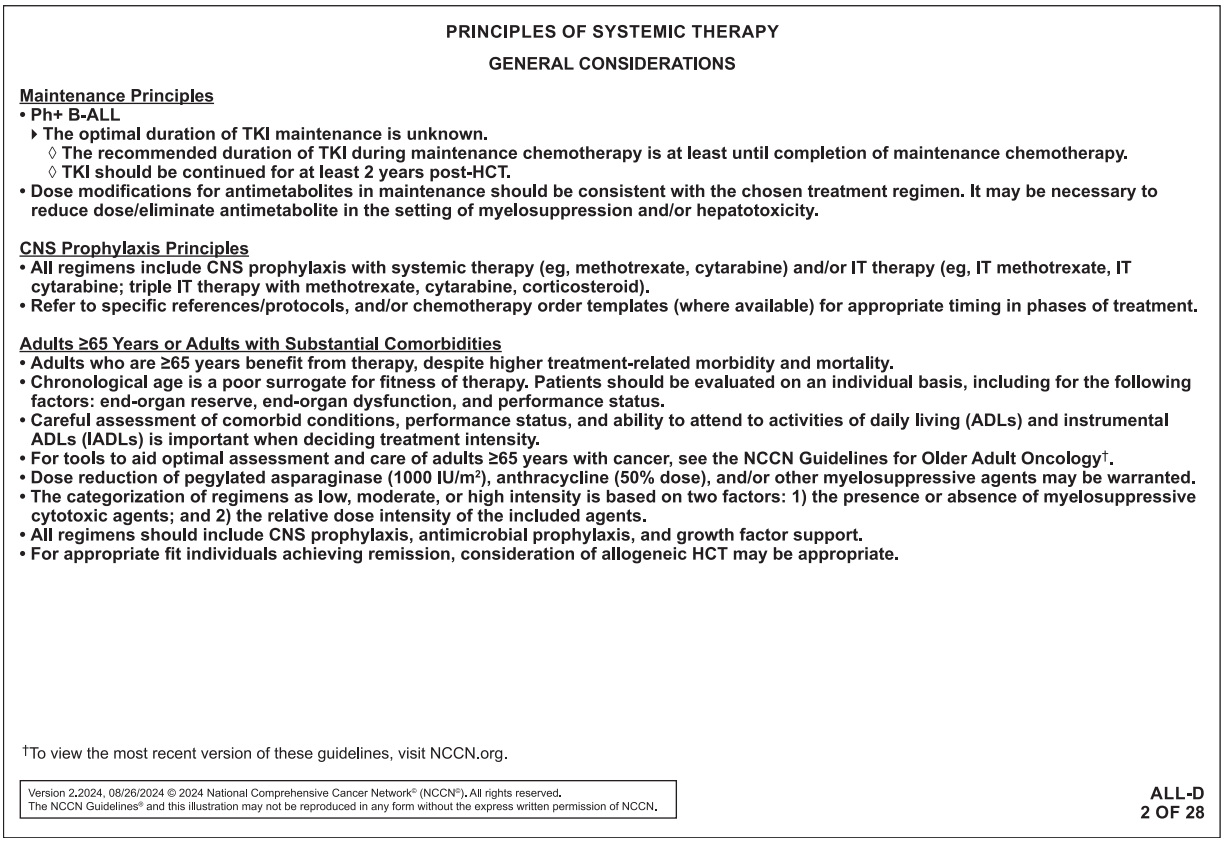

Figure 8. ALL-D 2 of 28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

median OS was not reached; the 5-year OS rate was 51%.[48] Thus, it appears that in patients with Ph-negative high-risk disease, allogeneic HCT in first CR improved DFS outcomes, whereas autologous HCT did not result in significant benefit compared with chemotherapy alone.

In the PETHEMA ALL-93 trial, adult patients with high-risk ALL [defined as having at least one of the following criteria: 30–50 years of age; WBC count ≥25 × 10^9/L; presence of t(9;22), t(4;11), or other 11q rearrangements; and t(1;19)] received post-remission induction therapy (n=222 eligible; median age, 27 years; range, 15–50 years) with allogeneic HCT (n=84; if matched related donor available), autologous HCT (n=50), or chemotherapy alone (n=48).[49] Based on intent-to-treat analysis of data from patients with Ph-negative high-risk disease, no significant advantage was observed in a donor versus no-donor comparison of median DFS (21 vs 38 months), median OS (32 vs 67 months), 5-year DFS rate (37% vs 46%), or 5-year OS rate (40% vs 49%). In addition, when the analysis was conducted based on the actual postremission treatment received, no significant differences were noted between treatment arms for 5-year DFS rates (50% for allogeneic HCT; 55% for autologous HCT; and 54% for chemotherapy alone).[49]

The role of allogeneic HCT in adults with ALL was also evaluated in the large multicenter MRC UKALL XII/ECOG E2993 study (n=1,913; age range, 15–59 years).[50] In this study, high risk was defined as ≥35 years of age; time to CR >4 weeks from induction; elevated WBC counts (>30 × 10^9/L for B-ALL; >100 × 10^9/L for T-ALL); or the presence of Ph chromosome. All other patients were considered to have standard-risk disease. Patients experiencing a remission with induction therapy were eligible to undergo allogeneic HCT if a matched sibling donor was available or, in the absence of a sibling donor, were randomized to undergo autologous HCT or chemotherapy. The 5-year OS rate was higher for patients randomized to chemotherapy alone compared with autologous HCT (46% vs 37%; P=.03). A donor versus no-donor comparison in all patients with Ph-negative ALL showed that the 5-year OS rate was significantly higher in the donor group than in the no-donor group (53% vs 45%; P=.01). This advantage in OS outcomes for the donor group was observed for patients with standard-risk disease (62% vs 52%; P=.02) but not for those with Ph-negative high-risk disease (41% vs 35%).[50] This was partly because of the high rate of nonrelapse mortality observed with the donor group compared with the no-donor group in patients with high-risk disease (36% vs 14% at 2 years). Among patients with standard-risk disease, the nonrelapse mortality rate at 2 years was 19.5% for the donor group and 7% for the no-donor group. Relapse rate was significantly lower in the donor group than in the no-donor group for both patients with standard-risk disease (24% vs 49%; P<.001) and those with high-risk disease (37% vs 63%; P<.001).[50] Nevertheless, the high nonrelapse mortality rate in the donor group among patients with high-risk disease seemed to diminish the advantage of reduced risk for relapse in this group. This study suggested that allogeneic HCT in first CR was beneficial in patients with standard-risk ALL.

The benefit of matched sibling allogeneic HCT in adults with standard-risk ALL was also reported by the HOVON cooperative group. In a donor versus no-donor analysis of patients

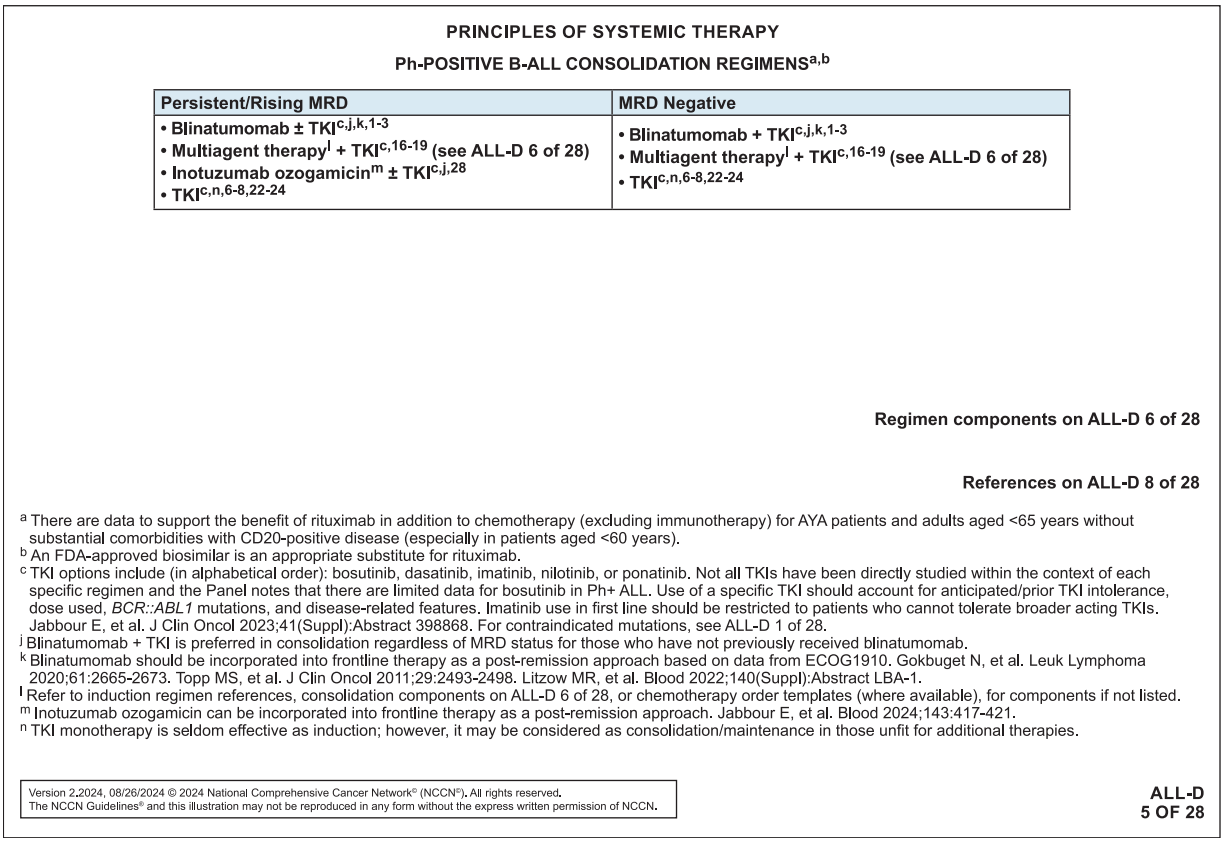

Figure 9. ALL-D 5 of 28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

with standard-risk ALL undergoing postremission therapy with matched sibling allogeneic HCT or autologous HCT, the donor arm was associated with a significantly reduced 5-year relapse rate (24% vs 55%; $P<.001$) and a higher 5-year DFS rate (60% vs 42%; $P=.01$) compared with the no-donor arm.[51] In the donor group, the nonrelapse mortality rate at 5 years was 16% and the 5-year OS rate was 69%.[51]

As evidenced by the previously described studies, matched sibling HCT has been established as a valuable treatment strategy for patients with both standard and high-risk Ph-negative ALL, but subsequent studies have examined the role of unrelated donor transplants in high-risk Ph-negative ALL. In a retrospective analysis of 169 patients who underwent unrelated donor HCT during first CR, 60 patients (36%) had one poor prognostic factor and 97 (57%) had multiple risk factors. The 5-year survival rate was 39%, which is higher than survival rates reported in studies of patients with high-risk disease receiving chemotherapy alone.[52] The most significant percentage of treatment-related mortality occurred in patients who were given mismatched donors compared with partially or well-matched donors. There was no significant difference in outcome between patients <35 years of age and patients >35 years of age, suggesting that unrelated transplants may be an option for patients who are older. In a follow-up retrospective study by the same group, reduced-intensity chemotherapy (RIC) was evaluated to lower treatment-related mortality.[53] RIC conditioning most commonly comprised busulfan (9 mg/kg or less), melphalan (150 mg/m^2), low-dose total body irradiation (<500 cGy single dose or <800 cGy fractionated), or fludarabine plus total body irradiation of 200 cGy. RIC is more prominent in the treatment of patients who are older; therefore, the median age for patients receiving full-intensity (FI) conditioning was 28 years (range, 16–62 years), and for patients receiving RIC, the median age was 45 years (range, 17–66 years). Despite the variation in age, results from the study have shown no difference in relapse (35% vs 26%, $P=.08$) or in treatment-related mortality (FI, 33%; 95% CI, 31%–36% vs RIC, 32%; 95% CI, 23%–43%; $P=.86$) at 3 years.[53] The 3-year survival for HCT was similar following first CR (FI, 51%; 95% CI, 48%–55% vs RIC, 45%; 95% CI, 31%–59%) and second CR (FI, 33%; 95% CI, 30%–37% vs RIC, 28%; 95% CI, 14%–44%). The DFS was similar in both groups after first CR (FI, 49%; 95% CI, 45%–53% vs RIC, 36%; 95% CI, 23%–51%) and in second CR (FI, 32%; 95% CI, 29%–36% vs RIC, 27%; 95% CI, 14%–43%).[53]

A retrospective study of 576 adults ≥45 years of age compared RIC or myeloablative conditioning allogeneic HCT from HLA-matched siblings.[54] Patients who received RIC (n=127) versus myeloablative conditioning (n=449) did not show any statistically significant difference in leukemia-free survival ($P=.23$; HR, 0.84), thereby supporting the incorporation of more aggressive treatments for this population.[54]

A systematic review and meta-analysis of published randomized trials on postremission induction therapy in adults with ALL reported a significant reduction in all-cause mortality with allogeneic HCT in first CR (relative risk, 0.88; 95% CI, 0.80–0.97) compared with autologous HCT or chemotherapy.[55] A subgroup analysis showed a significant survival advantage

PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL CONSOLIDATION COMPONENTS[a,b,f,g,h,i]

AYA Patients without Substantial Comorbidities	Adults <65 years without Substantial Comorbidities	Adults ≥65 Years or Adults with Substantial Comorbidities
CALGB 10701[4,5] **+ TKI**[c]**:** Cytarabine, etoposide		
EsPhALL[18,20,21] **+ TKI**[c]**:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, etoposide, ifosfamide, high-dose methotrexate, pegaspargase, vincristine		**EWALL**[27] **+ TKI**[c]**:** Cytarabine, high-dose methotrexate, pegaspargase
Dose-adjusted HyperCVAD[9-13] **+ TKI**[c]**:** Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine		
Other multiagent therapy[16-19] **+ TKI**[c]**:** Cytarabine, high-dose methotrexate, methylprednisolone		
Vincristine + dexamethasone + TKI[14]**:** Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, high-dose methotrexate, vincristine		

References on ALL-D 8 of 28

[a] There are data to support the benefit of rituximab in addition to chemotherapy (excluding immunotherapy) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[b] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[c] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. J Clin Oncol 2023;41(Suppl):Abstract 398868. For contraindicated mutations, see ALL-D 1 of 28.
[f] All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
[g] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.
[h] For patients who develop hypersensitivity to E. coli-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[i] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤21 years for more sustained asparaginase activity. Silverman LB, et al. Blood 2016;128:175; Angiolillo AL, et al. J Clin Oncol 2014;32:3874-3882.

ALL-D 6 OF 28

Figure 10. ALL-D 6 of 28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia, Version 2.2024.

with allogeneic HCT in standard-risk ALL, whereas a nonsignificant advantage was seen in high-risk ALL.[54] Autologous HCT in first remission was not shown to be beneficial relative to chemotherapy in several large studies and meta-analyses.[48,50,55,56]

NCCN Recommendations

For adults with Ph-negative B-ALL, regardless of risk group, the NCCN ALL Panel recommends treatment in a clinical trial, where possible. In the absence of an appropriate clinical trial, the recommended treatment approach would initially depend on the patient's age and/or presence of comorbid conditions. Although the age cutoff indicated in the guidelines for treatment decisions for adults has been set at 65 years, it should be noted that chronologic age alone is not a sufficient surrogate for defining fitness; patients should be evaluated on an individual basis to determine fitness for therapy based on factors such as performance status, end-organ function, and end-organ reserve (Figures 1 and 2).

In the absence of an appropriate clinical trial, recommended treatment regimens for patients <65 years of age and without substantial comorbidities include multiagent therapy regimens based on data from multi-institutional studies, such as the ECOG 1910 regimen, the GRAALL-2005 (with rituximab for CD20-positive disease), dose-adjusted CALGB 8811 Larson regimen, and MRC UKALLXII/ECOG 2993 regimen. Multiagent therapy protocols based on data from single-institution studies, including the USC/MSKCC ALL regimen based on CCG-1882, the Linker 4-drug regimen, dose-adjusted hyper-CVAD (with or without rituximab or sequential blinatumomab), and InO + mini-hyper-CVD (with or without sequential blinatumomab) are other recommended regimens (Figures 3–6).

Treatment regimens should include adequate CNS prophylaxis for all patients. It is important to adhere to the treatment regimens for a given protocol in its entirety. Testing for *TPMT* gene polymorphism should be considered for patients receiving 6-MP as part of maintenance therapy, especially in those who experience severe bone marrow toxicities (Figures 7 and 8).

For patients experiencing a CR following initial induction therapy, MRD status should be assessed (see ALL-F in the full guidelines, available online at NCCN.org). If the resulting MRD status is negative or unavailable, consolidation therapy should consist of continuation of the multiagent therapy protocol or blinatumomab monotherapy, followed by maintenance therapy. Blinatumomab should be incorporated into frontline multiagent therapy regimens as a postremission approach based on data from ECOG1910.[57] Consolidation with allogeneic HCT may also be considered, especially in the setting of high-risk features, such as age >35 years, presenting WBC >30 × 10^9/L, or poor-risk cytogenetic or molecular alterations, including but not limited to complex karyotype, hypodiploidy, *TP53* mutation, *PAX5alt*, and alterations of *IKZF1* (see ALL-3 in the full guidelines, available online at NCCN.org). For patients with negative MRD by flow cytometry but positive MRD by an FDA-approved next-generation sequencing assay, repeat testing before consolidation is started should be considered to confirm MRD status. If MRD status is unavailable, consideration should be made for retesting MRD at the first available opportunity (Figures 1, 2, 9, and 10).

If MRD is persistent or rising, blinatumomab or InO are recommended, though blinatumomab is preferred in this setting for those who have not previously received blinatumomab. Although long-term remission after blinatumomab monotherapy is possible, allogeneic HCT can be considered as consolidative therapy. Although data are limited, it is recommended to wait at least 4 weeks from InO monotherapy and the start of conditioning for allogeneic HCT to minimize risk of SOS. SOS has been shown to occur less frequently when less alkylators are used as part of the conditioning regimen (Figures 1, 2, 9, and 10).[58]

Adequate count recovery per protocol is necessary before transitioning to postremission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow up for MRD may be warranted (Figures 1 and 2).

In all cases, the optimal timing of HCT is unclear. For patients who are fit, additional therapy is recommended to eliminate MRD before transplant (Figures 1 and 2).

For patients experiencing less than a CR after initial induction therapy (ie, presence of primary refractory disease), the treatment approach would be similar to that for patients with relapsed/refractory disease (Figures 1 and 2).

For patients with Ph-negative B-ALL (regardless of risk group) ≥65 years of age or with substantial comorbidities, in the absence of an appropriate clinical trial, recommended induction therapy includes multiagent therapy regimens, InO monotherapy as per ALLIANCE A041703 (a category 2B recommendation), or palliative corticosteroids (Figures 1 and 2). Multiagent therapy recommendations are broken down by intensity. Low intensity options include vincristine and prednisone or POMP. Moderate intensity regimens include ALLOLD07 (PETHEMA-based regimen), the EWALL, GMALL, or GRAALL regimens, or a modified DFCI 91-01 protocol. Rituximab is added to the GMALL regimen for CD20-positive disease. Immunotherapy regimens classified as moderate intensity include ALL-INITIAL-1 (InO/dexamethasone) and InO + mini-hyper-CVD. High intensity regimens include CALGB 9111, ECOG 1910, and dose-adjusted hyper-CVAD. Dose modifications may be required for systemic therapy agents, as needed. MRD assessment and consolidation approach after initial treatment induction would be similar to that for adults <65 years of age with Ph- B-ALL, with appropriate dose modifications (Figures 8–10).

Summary

The management of ALL includes complex, intensive multiagent chemotherapy regimens, broken down into treatment phases including induction, consolidation, and maintenance therapy. Induction regimens for adults with Ph-negative ALL are generally based on a backbone of vincristine, corticosteroids, and anthracyclines. There have been dramatic improvements in outcomes for patients with ALL over the past several decades, in part due to incorporation of MRD testing into treatment protocols and the development of novel therapies, such as blinatumomab and InO, which are becoming an increasingly important part of the frontline treatment landscape. Although chronological age is a factor in the choice of frontline therapy, the NCCN panel advocates for shared decision making and treatment decisions based on additional factors such as comorbid medical conditions, performance status, and end-organ function/reserve.

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